

REMARKS

The present invention is directed to a new and unobvious combination of specified retinoids and specified retinoid boosters **in a dual compartment package, where the compartments are joined together and made of aluminum**, intended to avoid chemical degradation of retinoids that would be caused by contact with the retinoid boosters. The specified retinoid boosters, despite boosting the effect of specified retinoids on the skin, tend to *destabilize* the specified retinoids in the composition. The claimed retinoid boosters are among a specific list that has been demonstrated with objective evidence on p 37 of the Specification and in the Rule 132 Declaration to de-stabilize retinoids to a greater extent than the retinoids would be unstable in the absence of the boosters, i.e., there is a greater stability problem. **The 2d column of the Table on p 37 lists the fold increase in rate of retinol loss compared to retinol without booster.** The retinoid/retinoid booster combinations, *both of which are intended for the same skin benefit and to be applied substantially at the same time*, are maintained in separate compartments of a package and the retinoid composition is kept out of contact with oxygen to promote its stability against chemical degradation and to avoid further instability that would be caused by contact with retinoid boosters.

The independent claims herein are further limited by dependent claims, some of which, i.e., 2, 7 and 12, are directed to retinoid combinations with *at least 2 boosters*. *Claims 5, 10, and 15 are directed to a method of mimicking the effects of retinoic acid using the products of the independent claims.* An unexpected result of the present invention is that compositions that do not contain retinoic acid behave analogously to treatment with retinoic acid (i.e. mimic), as if they did contain the most active form of retinoid, i.e., retinoic acid, while maintaining retinoid stability over time.

Claims 1 -2, 4-7, 9-12 and 14-18 Are Not Obvious under 35 USC § 103

Claims 1-2, 4-7, 9-12, and 14-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Burger et al. (USPN 5,759,556) *and Granger 5,716,627* in view of Liu et al. (USPN 5,976,555) and Soares et al. (USPN 5,914,116) and further in view of Remington's Pharmaceutical Sciences (Remington). Applicants respectfully traverse. *Burger '556* and *Granger '627* do not render the present invention obvious alone or in combination with the secondary references.

According to the Office Action, Burger '556 disclose a skin conditioning composition comprising a compound selected from retinol or retinyl ester in combination with *alpha-ionones and damascones*; Granger '627 disclose retinoids, *fatty acids* and *amides*. *Undisputably*, Burger et al. and Granger et al. *fail to* disclose the first compartment for storing retinol or retinyl ester kept out of contact with oxygen, and the second compartment for storing boosters (e.g., *alpha-ionone*), and the first and second compartments being joined together; and avoiding chemical degradation of retinol or retinyl ester in the first composition that would be caused by contact with boosters (e.g., *alpha-ionone*) in the second composition.

Liu et al. and Soares et al., *alone, combined, or in combination with Remington's*, do not remedy the deficiencies of Burger et al. and Granger et al. In fact, none of the references cited in the Office Action teach or suggest the need or the solution for stabilizing retinoid compositions in the presence of retinoid enhancing actives. *None of the references teaches or suggests that boosters destabilize retinoids to a greater degree that retinoids alone would be unstable, and therefore none of the references*

teaches or suggests a solution, in particular, a dual compartment container made of aluminum. Therefore, although dual purpose single formulation cosmetic products have been developed in the cited art, only in hindsight, with the benefit of the disclosure of the present invention, is the need for stable cosmetic compositions that attenuate the existing problems of retinoid stability in the presence of boosters met.

Liu et al. *at most* merely restate the problem *and fail to address the further instability contributed to retinoids by the presence of boosters.* Liu et al. *at most* merely state an invitation to invent by restating that retinoids are unstable. **Liu et al. do not address** the problem to which the present invention is addressed, i.e., **alleviating the additional instability contributed by boosters.** (At most, Liu et al. provide a different solution – i.e. formulating in an emulsion with a specifically defined stabilizer system, but all in one composition.) The combination cited references does not arrive at the subject matter of the present invention as claimed. Although Liu et al. describe a container for storing the composition so that it is out of contact with oxygen, the container is described in combination with a retinoid composition with an emulsifier system and a co-emulsifier alone and does not protect the retinoid from degradation due to contact with retinoid boosters.

Further according to the Office Action, Soares et al. (USPN 5,914,116) teaches a first and second composition stored in separate containers joined together. However, *the product of Soares et al. includes a first composition for obtaining a first skin benefit (e.g., Vitamin A palmitate) and a second composition for obtaining a second and different benefit, "the first and second actives and benefits being different from one another;" and the two compositions are part of a regimen teaching their application at different times of day.* See Col. 2, lines 1-5. The Office Action admits that Soares et al.

(USPN 5,914,116) does not teach that the first and/or second compartments keep the respective compositions out of contact with oxygen, neither does it teach that the two compartments are made of aluminum, *nor does it teach the two compositions aimed at the same skin benefit and intended to be applied at substantially the same time.*

As discussed above, Burger et al and Granger et al. are insufficient primary references and the secondary references do not remedy its deficiencies. Furthermore, there is no motivation to combine Burger and Granger with Remington, Soares et al. and Liu et al. Remington at p. 1511 admits, "The choice of containers and closures can have a profound effect on the stability of many pharmaceuticals."

Accordingly, it would not have been obvious to a person of ordinary skill in the art at the time the invention was made to employ two compartments for separately storing retinol or retinyl ester in a first composition and booster in the second composition in order to stabilize retinoids against the instabilities caused by the presence of boosters. Dimethyl imidazolidone cited on page 5 of the Office Action is not relevant to the invention as presently claimed.

IN PARTICULAR, CLAIM 16 IS NOT OBVIOUS OVER THE MULTIPLE COMBINED REFERENCES

Claim 16 specifies a booster combination of **climbazole** (B5) with **alpha-ionone** (B1) and/or **damascenone**.

Burger '556 do not disclose *climbazole* and Granger '627 is cited for disclosing a skin conditioning composition comprising a) retinol or retinyl ester, b) azole, e.g., *climbazole*, c) a fatty acid amide such as linoleoyl-DEA. However, admittedly, Granger et al '627 does not disclose the first compartment for storing retinol or retinyl ester kept out of contact with oxygen, and the second compartment for storing azole (e.g. *climbazole*), and the first and second compartments being joined together; and avoiding chemical degradation of retinol or retinyl ester in the first composition that would be caused by contact with boosters (e.g. *climbazole* or *alpha ionone*) in the second composition.

As stated previously, the independent claim 11 and claim 16 dependent thereon relate to specific booster compounds that are shown to de-stabilize the claimed retinoids to a greater extent than the degree of instability in the absence of the boosters. See the table on page 37 of the Specification. For example, the results in the Table show that *alpha-ionone* increases the rate of retinol loss by a factor of 1.3. According to the accompanying Declaration, retinol is only 2/3 as stable in the presence of citral. Similarly, it can be seen that all the claimed boosters significantly increase the rate of retinol loss. Therefore, the **presence of the boosters necessitates separate compartments for the two compositions**, more so than the cited art. *These are unexpected results.*

EVIDENCE OF UNEXPECTED RESULTS HAS BEEN PRESENTED

Applicants have presented evidence of unexpected results in the Specification and accompanying Declaration. Independent claims 1, 6 and 11 relate to specific booster compounds that are shown to de-stabilize the claimed retinoids to a greater extent than the degree of instability in the absence of the boosters. See the table on page 37 of the Specification. For example, the results in the Table show that *alpha-ionone* (B1 booster) increases the rate of retinol loss by a factor of 1.3. **The data show that all the claimed boosters significantly increase the rate of retinol loss.** According to the accompanying Declaration, retinol is only 2/3 as stable in the presence of citral. Dr. lobst states that, based on analysis of the data presented, it is clear that Retinol stability is significantly diminished in the presence of boosters, creating a greater necessity for its stabilization than in the absence of boosters. Therefore, the presence of the boosters necessitates separate compartments for the two compositions, more so than the cited art. Neither Liu '555 nor Soares, nor any of the many cited references alone or in any combination, teaches nor suggests that boosters further destabilize retinoids. In other words, neither Liu '555 nor Soares, nor any of the many cited references alone or in any combination, suggest a way to protect the retinoid from degradation due to contact with retinoid boosters. The claimed invention is clearly not obvious in view of the cited art, and for the reasons above, the 103(a) rejections should be reconsidered and withdrawn. Additionally, Applicants have shown the advantages of employing more than a single booster with respect to increase in CRABPII production. **This advantage is supported by Dr. lobst's Declaration while demonstrating the instability due to the presence of boosters.**

These are

Invention Must Be Viewed As a Whole

It is improper to pick and choose pieces of a variety of art to come up with a rejection as in the Office Action. There must be some suggestion or motivation for combinations of the references, so as to come up with the claimed invention, which must be viewed as a whole.

Burger fails to disclose climbazole. Burger and Granger fail to disclose the first compartment for storing retinol or retinyl ester kept out of contact with oxygen; and first and second compartments being joined together; and avoiding chemical degradation of retinol or retinyl ester in the first composition. Nor do Burger, Liu and Soares disclose the first compartment made of aluminum. Remington's is cited for storage of pharmaceuticals to address the aluminum container limitation.

The Office Action position notwithstanding, Applicants respectfully submit that the significant diminution in retinoid stability in the presence of boosters was not known and is unexpected over Liu et al. and Soares et al. alone or in any combination with each other or the other cited references. Liu et al. and Soares et al. have nothing to do with boosters. On the other hand, the present invention teaches the need for stabilizing retinoids in the presence of boosters and evidence in the Examples of the Specification and in the Declaration provides objective support for the unobviousness of the present invention.

If fact, none of the references cited in the Office Action teaches or suggests the need or the solution for stabilizing retinoid compositions in the presence of retinoid enhancing actives. Therefore, although dual purpose single formulation cosmetic

products have been developed in the cited art, only in hindsight, with the benefit of the disclosure of the present invention, is the need for stable cosmetic compositions that attenuate the existing problems of retinoid stability in the presence of boosters met. There is no suggestion in the cited art that the further destabilization of retinoids contributed by the presence of boosters was within the knowledge which was within the level of ordinary skill at the time the claimed invention was made, nor that the knowledge was generally available to one skilled in the art. Even if combined, Applicants respectfully submit that, since the independent claims are in condition for allowance, those claims that depend from them are also in condition for allowance.

An obviousness rejection is proper only when “the subject matter as a whole would have been obvious at the time the invention was made ...” (emphasis added). 35 U.S.C. 103. Applicants respectfully submit that the Office Action has improperly chosen certain aspects of one reference and combined them with aspects of other references, without showing where the motivation is to combine them to come up with the subject matter of the present invention as a whole, within the meaning of 35 U.S.C. 103. Applicants submit that the pending claims are not obvious over the cited references, under 35 U.S.C. 103. Reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting Rejections Should Be Reconsidered and Withdrawn

Applicants traverse these rejections. Applicants respectfully maintain that the double patenting rejections under the judicially created doctrine of obviousness-type double patenting is improper for the reasons discussed above *with reference to the 103 rejection*. The inventions are not for the same basic concept. Nevertheless, in the interest of progressing the present application to issue without delay, to the extent any double patenting rejections may remain, Applicants would be willing to supply a terminal disclaimer upon indication of allowability of the present claims.

In view of the foregoing amendments and comments, Applicants request the Examiner to reconsider the rejection and now allow the claims.

If a telephone conversation would be of assistance, Applicant's undersigned attorney invites the Examiner to telephone at the number provided.

Respectfully submitted,



Ellen Plotkin
Registration No. 36,636
Attorney for Applicant(s)

(201) 894-2253